Express Mail Label No.: EV138530938US
Date of Deposit: February 25, 2003

Attorney Docket No. 15966-518 (CURA-18)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S):	Mehta et al.		
ASSIGNEE:	CuraGen Corporation		
SERIAL NUMBER:	09/351,617	EXAMINER:	P. Ponnaluri
FILING DATE:	July 12, 1999	ART UNIT:	1639
FOR:	General Screening Method for Ligand-Protein Interactions		

#26
1648
3-14-03

Branford, CT

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132

I, Thomas P. Jarvie, hereby declare and state as follows:

1. I am a named inventor of the above-identified application, and I am employed by CuraGen Corporation, the assignee of this application.

2. I am aware of the Examiner's November 25, 2002 Final Office Action. In particular, I understand that the Examiner contends that the chemical hybrid invention of the present application is anticipated by, or in the alternative, is obvious over the three-hybrid system of Licitra et al., Proc. Nat'l. Acad. Sci. USA (1996) 93:12817-2 ("Licitra") and U.S. Patent No. 5,928,868 ("Liu"). Specifically, the Examiner asserts that "Applicants have not shown how and why the bond between the ligand A and the target of the instant claimed method is different from the prior art." (Final Office Action mailed November 25, 2002, paragraph bridging pages 6 and 7).

3. The Examiner has admitted that Licitra and Liu do not teach that the binding of the ligand A to the target is irreversible. (See Office Action mailed March 12, 2002, page 9). Thus, the sole issue remaining is the Examiner's contention that "the bond between the ligand [A] and the target can be covalent irreversible or reversible based on several factors. The specification does not disclose the specific conditions required for 'irreversible covalent' bond formation between the ligand A and target." (Final Office Action mailed November 25, 2002, page 5). I make this declaration to address and rebut this contention.

not in the claims

4. The chemical hybrid system of the present invention requires that ligand A forms an irreversible covalent bond with its target. In my opinion, the conditions under which this irreversible covalent bond occurs are adequately disclosed in the as filed specification. To illustrate an embodiment of the chemical hybrid system of the present invention, I make reference to the schematic drawings shown in the attached Appendix A (Figures i - iv).

5. As shown in schematic i, the chemical hybrid system of the invention involves a hybrid molecule created by the linkage of ligand A and ligand B (labelled '**A**' and '**B**' throughout Appendix A). The invention also involves two fusion or hybrid proteins, each containing a target molecule for binding ligand A or ligand B (labelled '**X**' and '**Y**', respectively, throughout Appendix A) and a transcription module (labelled '**X**'', a DNA-binding domain and '**Y**'', a transactivation domain, respectively, throughout Appendix A); and a vector (labelled '**V**' throughout Appendix A) encoding a reporter protein, which is switched on in the presence of the two united transcription modules.

& X

Ligand A is specific — which is not in the claims

6. As shown in schematic ii, Ligand **A** has a specificity for pre-determined target **X** fusion protein such that **A** and **X** form an irreversible covalent bond upon binding. Those skilled in the art will recognize that, under physiological conditions, covalent bonds are irreversible. *See* Lodish et al., Eds., MOLECULAR CELL BIOLOGY, 4th ed., Chapter 2.1 (1999).

7. As shown in schematic iii, once Ligand **A** forms an irreversible covalent bond with its target **X** fusion protein, the chemical hybrid system of the invention resembles a classical two-hybrid system, in which Ligand **B**, which has an affinity for the target **Y** fusion protein, binds to the target **Y** fusion protein. In the chemical hybrid system of the invention, the affinity of ligand **B** for target **Y** may vary substantially. This is significant in that the chemical hybrid system of the invention, unlike the three hybrid system of Licitra and Liu, is capable of measuring the K_d of the binding of Ligand **B** to the target **Y** fusion protein

8. As shown in schematic iv, when Ligand **A** is bound to target **X** fusion protein by virtue of an irreversible covalent bond, and Ligand **B** binds to the target **Y** fusion protein, the reporter gene is switched on.

9. As stated above, in contrast to the three hybrid systems of Liu and Licitra, the irreversible covalent binding of Ligand **B** to the target **X** fusion protein causes the chemical hybrid system of the invention to resemble a two hybrid system. This difference results in a decrease in the system noise such as the non-hybrid ligand-mediated binding observed in the three hybrid systems of Liu wherein protein hybrid #1 binds directly to protein hybrid #2 in the absence of the ligand hybrid. Further, the chemical hybrid system of the invention allows for lower concentrations of the hybrid ligand to be used and is thus more effective (*e.g.*, when the hybrid ligand is cytotoxic or cytostatic to the host cell) and more economical, and furthermore, allows a determination of the K_d of the binding of Ligand **B** to the target **Y** fusion protein, none of which are possible with the methods of Liu and Licitra.

10. Thus, for all the foregoing reasons, it is my opinion that the pending claims are not anticipated by or obvious in view of Licitra and/or Liu. Thus, that the Examiner should withdraw the rejection and allow the pending claims.

11. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18, United States Code, and that willful false statements may jeopardize the validity of this application and any patent issuing therefrom.

Thomas P. Jarvie
THOMAS P JARVIE

Signed at Branford, CT
this 29th day of January